A

Synopsis

On

HARMONIZATION OF BIOSIMILAR DRUG APPROVAL PROCESSES: CHALLENGES, PROGRESS, AND FUTURE DIRECTIONS IN REGULATORY AFFAIRS FOR STRINGENT MARKETS

Ph.D. (Pharmaceutical Sciences)

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1.0 Introduction: To ensure timely prompt access to biosimilar medications that can save lives, especially those used to treat autoimmune disorders, cancer, and other severe illnesses. Simplifying the approval procedures is crucial in markets that are subject to strict regulations, including the US, EU, and those that adhere to WHO norms. Many other nations frequently utilize these legislative regimes as models, particularly in the developing world.[1]

Through collaborative registration procedure and Asian joint assessment procedures, the WHO not only sets global standards but also facilitates regulatory paths. Products in the Rest of the World (ROW) market, which includes middle-income nations as well as places like Africa and ASEAN, benefit greatly from this strategy. Manufacturers can shorten time to market and increase access to essential treatments by utilizing WHO prequalification and reliance models.[2]

Additionally, during public health emergencies such as pandemics, the WHO supports equitable access by providing life-saving drugs to low-income countries through donation programs, emergency use listings (EUL), and pooled procurement mechanisms.[3]

1.1 Dossier filling and Approval Harmonization: To critically examine the current landscape of regulatory harmonization in drug approval processes among stringent regulatory authorities US FDA, Europe, WHO (SRAs), with a focus on identifying key challenges, evaluating progress made through global initiatives (such as ICH and Project Orbis, Asian Joint assessment, WHO collaborative registration procedure), and exploring future directions for achieving greater regulatory convergence specially for life saving drugs and advance dosage form like Biosimilar.[4]

1.2 Biosimilar drugs: Biosimilar medications are biological products that are very similar to an approved biological treatment (the "reference product") and do not differ clinically.

. They are not identical copies like generic drugs, as they are made from living cells and are more complex than chemically synthesized drugs. Biosimilars are approved based on rigorous standards demonstrating similarity in quality, safety, and efficacy to the reference product[5,6]

Biosimilar definition as per US FDA, EMA, WHO & CDSCO

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US FDA	EMA	WHO	CDSCO
Biosimilar Goods A biosimilar is a biological product that is very comparable to an already-approved reference product from the FDA and does not differ clinically.	A biosimilar is a biological medication that is very similar to another biological medication that has already received approval (the "reference medicine").The same pharmaceutical quality, safety, and efficacy requirements that apply to other biological medications are used to approve biosimilars.	The World Health Organization (WHO) defines a biosimilar as a "biotherapeutic product that is similar to an already licensed reference biotherapeutic product in terms of quality, safety, and efficacy."	A similar biologic product is one that, according to comparability, is comparable to an authorized reference biological product in terms of quality, safety, and efficacy.

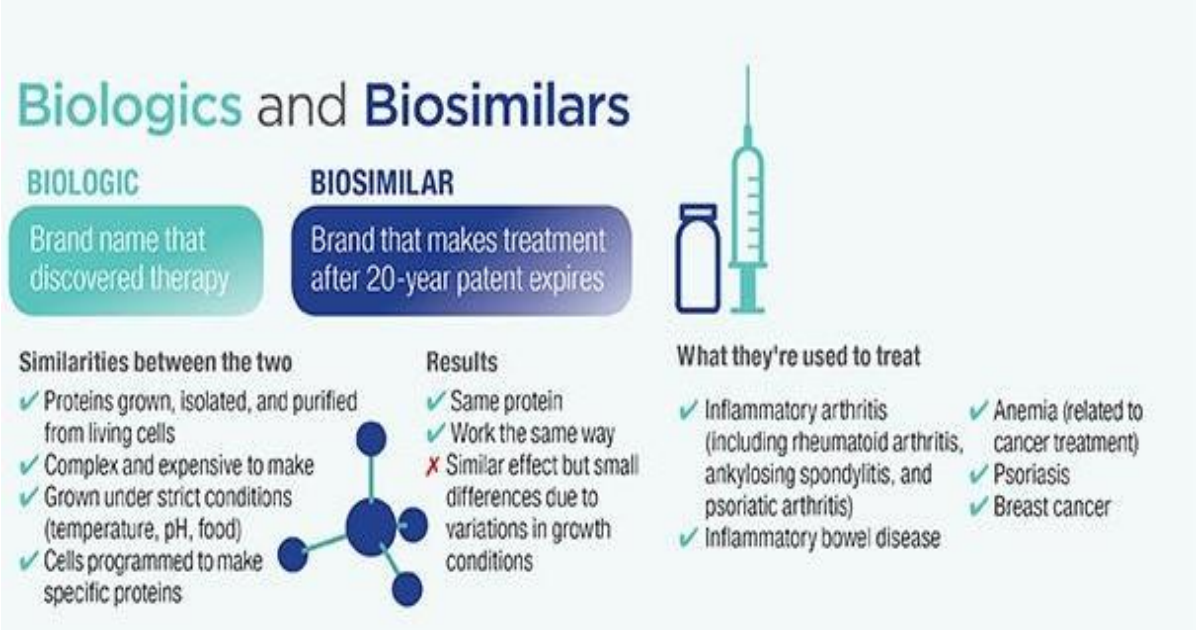
Biologics and Biosimilars
BIOLOGIC
Brand name that discovered therapy
BIOSIMILAR
Brand that makes treatment after 20-year patent expires
Similarities between the two
✓ Proteins grown, isolated, and purified from living cells
✓ Complex and expensive to make
✓ Grown under strict conditions (temperature, pH, food)
✓ Cells programmed to make specific proteins
Results
✓ Same protein
✓ Work the same way
✗ Similar effect but small differences due to variations in growth conditions
What they're used to treat
✓ Inflammatory arthritis (including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis)
✓ Inflammatory bowel disease
✓ Anemia (related to cancer treatment)
✓ Psoriasis
✓ Breast cancer

Fig.no.-1 Biologic and Biosimilars difference.

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1.3 Biosimilar share growth in US, EU and WHO. At a cumulative annual growth rate (CAGR) of 40.2%, the biosimilars market in the United States is expected to rise significantly from its 2021 valuation of USD 6.73 billion to USD 100.75 billion by 2029. [7]

The European biosimilars market is also experiencing strong growth, with a projected CAGR of 17.1% from 2025 to 2033, reaching a value of USD 59.73 billion by 2033 from USD 13.86 billion in 2024. [8]

The biosimilar market is expanding in both the US and Europe due to a number of causes. Major biologics' patent expirations are opening the door for biosimilars to reach the market. The need for more reasonably priced treatment alternatives is being driven by the rising incidence of chronic illnesses including cancer and autoimmune disorders.

Favorable regulatory frameworks, particularly in Europe, are supporting biosimilar approvals and market access.

The World Health Organization (WHO) promotes biosimilars globally as a way to increase access to essential biological medicines. The WHO's Essential Medicines List includes quality-assured biosimilars as safe, effective, and cost-effective alternatives. The WHO also supports voluntary licensing, regulatory harmonization, and education to promote biosimilar use. [9]

1.4 Research Gap: Despite on-going global efforts, the drug approval landscape remains fragmented, particularly among stringent regulatory authorities (SRAs), each operating under distinct legal, scientific, and procedural frameworks. This lack of harmonization leads to inefficiencies such as duplicated regulatory reviews, extended time-to-market for innovative therapies, and uneven access to essential lifesaving medicines or newly develop dosage form like Biosimilar across regions. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is one project that and Project Orbis have demonstrated potential in fostering regulatory convergence, their implementation varies significantly among jurisdictions, and key barriers such as divergent national policies, limited resource alignment, and inconsistent interpretation of standards persist.[10–12]

This study addresses the critical need to systematically analyze the challenges hindering full harmonization, assess the real-world progress of current convergence mechanisms, and explore strategies to advance mutual recognition, reliance models, and digital integration. By doing so, it seeks to highlight pathways to streamline regulatory processes, reduce redundancies, and support timely access to safe, effective, and high-quality medicines globally.[13]

1.5 Background Research:

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- **Reference Biotherapeutic product:** The US and EU regulatory authorities do not recognize Reference Listed Drugs (RLDs) approved outside their respective jurisdictions for the purpose of generic drug applications. Only RLDs approved by their own agencies are acceptable.[14]
- The US & EU does not recognize the other than own Reference Listed Drug (RLD) for the purpose of generic drug applications; only self -approved RLDs are acceptable.[15]
- **Interchangeability:** The ability of a biosimilar or generic medication to be used in place of the reference product without the involvement of the prescribing healthcare provider and yet produce the same clinical outcome in a particular patient is known as interchangeability.
- **In the U.S. (FDA):** Beyond bio similarity, an interchangeable biosimilar need to provide evidence that switching between the biosimilar and the reference product does not increase the risk of safety or efficacy.
- In **the EU (EMA):** Biosimilars are not designated as interchangeable by the EMA; member states make the choices on substitution and interchangeability.
- Bridging studies: To study and reduce the Bridging studies [16]
- Functional characteristic- Minor structure difference not lead to clinical difference.[17–18]

Table.1 Biosimilar dossier filing format in US, EU and WHO[19,20,21]

CTD	Section	US FDA	EU FDA	WHO	CDSCO
Module 1	Regional Administration	Form 356h, US labelling. REMS, Patent certification, BPCIA, PHS Act	EU application form, RMP	Country specific forms, WHO style labelling	Form 44, treasury challan, licensing details.
Module 1	Product Information	Labelling with 4-letter suffix, no originator data	SmPc, PIL, EU labelling format, includes originator data	Flexible per local needs	Labels, samples to Central Drugs Laboratory
Module 2	2.3Quality overall summary	Detailed CMC + analytical similarity summary	Full comparability data, product-specific guideline alignment	Process-focused; aligned with SRA practices	Summary of drug substance and Drug product
Module 2	2.4 Nonclinical Overview	Nonclinical waiver often needed	Toxicity usually required (1 species)	May be waived if strong analytics	Non-clinical Summary
Module 2	2.5Clinical Overview	Justify extrapolation, immunogenicity, PK/PD	Justify extrapolation based on MoA, safety. PK/PD	Same as EMA; adjusted for LMICs	Overview of clinical studies
Module 2	2.6 Nonclinical written/tabulated	In vitro assays required, in vivo may be waive	Comparative toxicity in 1 relevant species.	Required but waiver possible	Overview of immunogenicity
Module 2	2.7Clinical summary	PK/PD, switching studies for interchangeability	PK/PD, comparative efficacy, immunogenicity	Flexible, focus on PK/PD if efficacy not feasible	summary of pharmacokinetics

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Module 2	Summaries (2.3-2.7)	Totality of evidence emphasized	Stepwise approach; high comparison comparability demand	Stepwise and flexible for access	Summary of clinical studies of immunogenicity
Module 3	3.2.SDrug Substance	Strict COAs, comparability to US reference product	Must align with EU reference; comparability studies characterization,	High-level comparability to SRA-authorized products	Extensive characterization of the biosimilar vs the reference biologic
Module 3	3.2.P Drug Product	Full specs, container closure, process validation Detailed CMC; robust analytical similarity data needed	Full CMC with EU GMP compliance	Manufacturing and stability per WHO access needs Follows ICH Q5E, WHO biosimilar guidance	Detailed information on cell lines, fermentation, purification, formulation, stability data, and quality controls.
Module 3	3.2.R Regional Information	Comparability protocols, bridging data summaries	QP declaration, EU GMP certs	Manufacturing site and national certificates	Batch record
Module 4	Nonclinical	Required only if analytics are insufficient	Comparative studies generally required, Usually limited or waived	May be waived based on data Encourages in vitro, animal only if essential	In-vivo and in-vitro studies for safety, PD, PK, and toxicity.
Module 5	Clinical	PK/PD, immunogenicity switching study if interchangeability, bridging studies, Justify extrapolation	Comparative efficacy unless strong PD markers, Totality of evidence; PK/PD central, extrapolation allowed	PK/PD focus; efficacy only if needed. May allow data from reference-authorized comparators in other countries, extrapolation allowed	Comparative PK/PD, efficacy, immunogenicity; waivers possible if justified Extrapolation Indications Allowed with scientific rationale Periodic Safety Update Reports, pharmacovigilance plan, RMP

REMS-Risk evaluation and mitigation strategies BPCIA: Biologics Price Competition and Innovation Act
RMP: Risk management plan LMICs : Low- and Middle-Income Countries

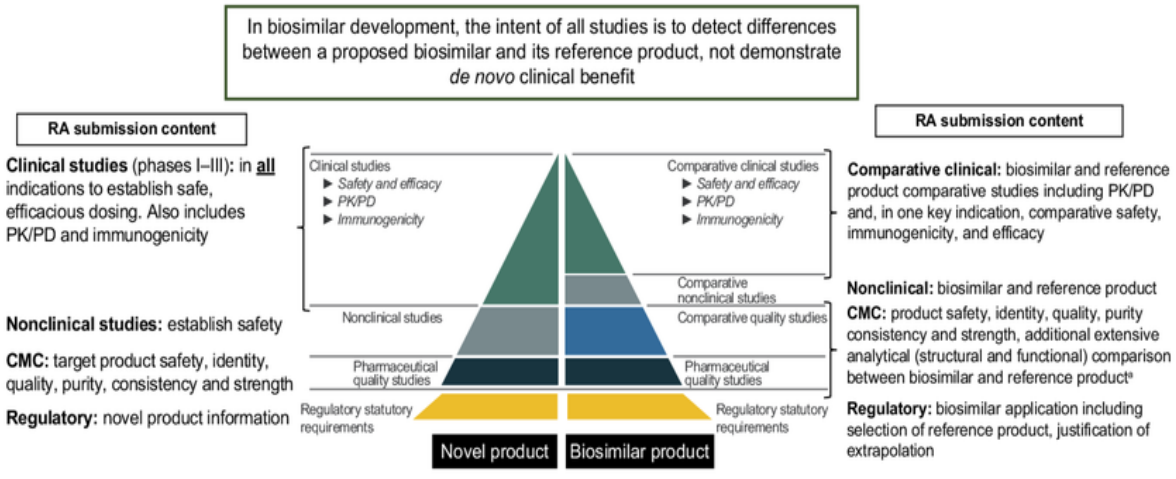
In biosimilar development, the intent of all studies is to detect differences between a proposed biosimilar and its reference product, not demonstrate de novo clinical benefit
RA submission content
Clinical studies (phases I–III): in all indications to establish safe, efficacious dosing. Also includes PK/PD and immunogenicity
Nonclinical studies: establish safety
CMC: target product safety, identity, quality, purity, consistency and strength
Regulatory: novel product information
Clinical studies
Safety and efficacy
PK/PD
Immunogenicity
Nonclinical studies
Pharmaceutical quality studies
Regulatory statutory requirements
Novel product
Comparative clinical studies
Safety and efficacy
PK/PD
Immunogenicity
Comparative nonclinical studies
Comparative quality studies
Pharmaceutical quality studies
Regulatory statutory requirements
Biosimilar product
RA submission content
Comparative clinical: biosimilar and reference product comparative studies including PK/PD and, in one key indication, comparative safety, immunogenicity, and efficacy
Nonclinical: biosimilar and reference product
CMC: product safety, identity, quality, purity consistency and strength, additional extensive analytical (structural and functional) comparison between biosimilar and reference product[a]
Regulatory: biosimilar application including selection of reference product, justification of extrapolation

Fig. no. 2 The biosimilar filling requirement with comparison biologic drug

1.6 Objectives of the study:

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- To identifying key challenges during dossier filling in US, EU and WHO.
- To evaluating progress made through global initiatives for Dossier filing.
- To transparent and harmonized regulatory processes for dossier filing and approval.
- To reduce approval timelines and cost of product approval from SRAs markets. .
- To increase review standards across US, EU and WHO regions.
- To identify and prioritize lifesaving drugs and advanced dosage forms such as biosimilars and new delivery systems for rapid distribution, ensuring timely and affordable access for patients.[22–24]

Table. 2 Some approved Biosimilar products in US, EU and WHO[25–26]

S.No	Europe	Disease	US	Disease	WHO	Disease
1.	Avzivi (Bevacizumab) Eurofins Pharma Quality Control France	Cancer	Jubbonti and Wyost (denosumab-bbdz) Sandoz Inc. Princeton, NJ U.S.	Prevent bone events in cancer	Rituximab Sandoz GmbH Austria	Cancer
2.	Ituxredi (Rituximab) Betapharm Arzneimittel GmbH Germany	Cancer	Fulphila (pegfilgrastim-jmdb) Mylan GmbH Zurich, Switzerland, U.S.	Infection during cancer treatment	Trastuzumab Samsung Bioepis NL B.V Netherlands	Breast cancer
3.	Tuznue (Trastuzumab) Kymos Pharma Services, S.L. Barcelona, Spain	Cancer	Ogivri (trastuzumab-dkst) Mylan GmbH Steinhausen, Switzerland	Certain breast and stomach cancers	Benzyl alcohol/Water for Injection + Trastuzumab Mylan Pharmaceuticals Private Limited	Cancer
4.	Absimky (Ustekinumab) Accord Healthcare Polska Poland	Immunology/ Rheumatology/Transplantation	Mvasi(Bevacizumab-awwb) Amgen Inc. One Amgen Center US	Treatment of cancer	Insulin Human Novo Nordisk as Denmark	Diabetes
5.	Avtozma (Tocilizumab) Celltrion Healthcare Hungary	Immunology/ Rheumatology/Transplantation	Wezlana (ustekinumab-auub) Amgen Inc. One Amgen Center Oaks US	Multiple Inflammatory Diseases	Adalimumab (therapeutic alternatives: certolizumab pegol, etanercept, golimumab,infliximab)Antirabies virus monoclonalantibodyes	Crohndisease,juvenile idiopathic arthritis and rheumatoid arthritis Rabies post-exposure prophylaxis
6.	Eksunbi (Ustekinumab)	Immunology/	Tofidence (tocilizumab-bavi)	Treat adult and pediatric arthritis	Insulin Glargine Sanofi-Aventis Deutschland GmbH Germany	Diabetes

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	Samsung Bioepis Netherlands	Rheumatology/Transplantation	Biogen MA Inc. Cambridge U.S.			
7.	Fymskina (Ustekinumab) Formycon AG Fraunhoferstrabe Germany	Immunology/ Rheumatology/Transplantation	Semglee(Insulin glargine-yfgn) Mylan Pharmaceuticals Inc. U.S.A.	Insulin Product for Treatment of Diabetes		
8.	Imuldosa (Ustekinumab) Accord Healthcare Barcelona Spain	Immunology/ Rheumatology/Transplantation	Retacrit (epoetin alfa-epbx) Hospira, Inc., a subsidiary of Pfizer Inc., USA	Treatment of anemia		

2.0 Literature survey:

S. No	Key Findings	References
1.	They avoid doing needless (duplicate) bridging studies because they are aware of the requirements for first-in-human radiopharmaceutical applications in the US, EU, and Canada. They also accept reference products that have been licensed and sourced from other countries and exchange product information with other regulatory bodies.	**2**
2.	Recognized the necessity of facilitating patient access and reducing the total requirements for human use due to the lack of toxicity. Utilizing a "reliance" concept and/or collaborative review to evaluate and approve biosimilars	**3**
3.	Before a regulatory framework for biosimilar approval is established, the products that have already been approved are reviewed and reassessed.	**4**
4.	Acknowledge that attempts to harmonize between the European Medical Authority, Health Canada, and the U.S. Food and Drug Administration would expedite the process of advancing novel radiopharmaceuticals for clinical use.	**27-28**

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S. No	Key Findings	References
5.	Guidelines for the regulatory evaluation of biosimilars were released by the World Health Organization (WHO) in 2009, and the organization has worked hard to assist member nations in incorporating the guidelines' evaluation concepts into their regulatory procedures. Four major issues remain despite this effort, according to a recent WHO survey (conducted in 2019–2020): the country's lack of reference products, the quality of some biosimilars (and even more so with no innovator products), the practice of interchangeability and naming of biosimilars, and a lack of resources.	**29-31**
6.	Establishing proper regulatory monitoring for pharmacovigilance is crucial for spotting product issues and proving the safety and effectiveness of biosimilars' interchangeability.	**32-33**
7.	Varied nations and/or regions have varied regulatory strategies for assessing the therapeutic equivalency of multisource (or generic) pharmaceutical goods. By harmonizing these methods, fewer in vivo bioequivalence studies might be conducted and needless drug exposure to humans could be prevented. A deeper comprehension of the elements influencing product performance and the expectations of various regulatory bodies may encourage global harmonization for regulatory standards. In order to harmonize regulatory approaches for establishing therapeutic equivalency and interchangeability of multisource drug products, this workshop gave pharmaceutical scientists from academia, industry, and regulatory agencies a chance to have candid conversations about current regulatory issues and industry practices.	**34-36**
8.	Since they involve numerous organizations and nations and exhibit the highest level of harmonization, these international initiatives are significant undertakings. In order to reach a worldwide scientific agreement, the goal of this technical and scientific intergovernmental cooperation is to address scientific issues that support the decisions made by individual countries and international regulatory agencies. Facilitating the development of novel medications and making them accessible to as many people as possible globally are the objectives. Complete system and regulation integration is not the goal. These	**37**

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S. No	Key Findings	References
	projects' primary problem is managing the structure and its complexity because of the large number of participants (the World Health Organization [WHO] has 194 Member States) and the variety of requirements, difficulties, and developmental stages of its members.	
9.	A pharmaceutical product that has not been confirmed by trained professionals to be safe and effective under the particular circumstances listed, advised, or suggested on the label is referred to as a "new drug." This can include a brand-new chemical formula or an already-approved drug that is being used for a different purpose. Rules that need to be adhered to when regulating novel medications in difficult markets	**38-39**
10.	Since using a single strategy to ensure public health safety is nearly impossible and ineffective, many countries have their own regulatory bodies. Therefore, a company's regulatory affairs department is well-versed in each nation's rules to guarantee that the business complies with all applicable laws and regulations. By incorporating regulatory principles and creating and submitting the necessary regulatory dossiers to health authorities, Regulatory Affairs contributes to the development and marketing of new pharmaceutical products. Therefore, this page summarizes the application process for new and shortened drug approval in the USA, Europe, India, and Japan.	**40-42**
11.	Regulatory Affairs is crucial to ensuring the quality, safety, and effectiveness of pharmaceuticals, medical devices, and other healthcare products. As the healthcare industry evolves as a result of globalization, technology advancements, and new regulatory paradigms, it is imperative to predict future trends and challenges in regulatory affairs. The implications of emerging domains, such as gene therapies, digital health, artificial intelligence, and personalized medicine, for regulatory frameworks are examined in this abstract. It also discusses the growing importance of patient-centered methods, global harmonization, and real-world evidence in regulatory decision-making. It also examines the challenges posed by supply chain disruptions, cyber security threats, and regulatory ambiguity in a rapidly evolving world. By embracing innovation, teamwork, and flexible regulatory approaches, stakeholders	**43-44**

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S. No	Key Findings	References
	may successfully negotiate the complex regulatory environment of the future and enable the prompt supply of safe and efficient healthcare products to people around the globe.	
12.	The regulatory frameworks for biologics in the US and the EU differ but coincide in terms of what constitutes a biologic and the technical requirements for approval. In the United States, the term "biological product" has been around for a while, and historical context continues to shape how it is understood. In the European Union, biologics are mainly categorized according to their constituent parts and manufacturing methods. Despite these distinctions, both jurisdictions concur that biologics need special handling because of their special characteristics, including their intricate structures and susceptibility to alter throughout production. In the US, a separate act was approved by Congress for biologics, while in the EU, they are subject to the standard licensing process along with some particular constraints. Despite efforts by US and EU authorities to unify certain technical requirements for biologics applications, there is a great deal of overlap in the standards enforced by the two regions. From nonclinical trials to clinical trials and approval, this chapter provides a summary of the regulatory regimes in the US and the EU. After that, the essay discusses acceptances and rejections in the US and Europe.	**45**
13.	Assuring safety and efficacy while facilitating the swift passage of novel treatments through the regulatory and research processes are conflicting objectives in the regulation of medical medications and devices. Different strategies are used by the US and the EU to address these issues. The European Commission synchronized the laws of 28 separate nations when they joined to form the European Union, in contrast to the United States, which has traditionally depended on a highly centralized method through a single agency, the Food and Drug Administration (FDA).	**46**

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3.0 Methodology: Core Areas to Explore

3.1. Regulatory Convergence and Harmonization

Convergence - aligning standards without changing laws.

Convergence refers to the voluntary process by which regulatory authorities and stakeholders align their technical requirements, standards, and practices without the need to change existing national laws or regulations.

Harmonization - mutual recognition and coordinated standards.

International regulatory organizations are the backbone of global harmonization. Their efforts in mutual recognition and standard coordination ensure regulatory efficiency, facilitate innovation, and protect public health across borders.[47]

Analyze how different regions interpret and implement ICH guidelines.

Globally recognized standards for pharmaceutical quality, safety, effectiveness, and multidisciplinary practices are provided by the International Council for Harmonization (ICH). However, interpretation and implementation of these guidelines vary across regions due to differences in regulatory capacity, legal frameworks, health priorities, and political structures.

3.2. Case Studies

Harmonization of clinical study data requirements across regions.

Harmonizing clinical data requirements ensures that:

- Data from a single global trial can support regulatory submissions in multiple regions.
- Redundant studies are minimized, reducing costs and ethical burdens**.**
- Regulatory review and product approvals are accelerated.

Comparative analysis of the drug's approval across US FDA, Europe and WHO.

The approval process for the same pharmaceutical product can differ significantly between SRAs countries (e.g., US, EU, WHO), due to variations in regulatory frameworks, resources, and alignment with international standards.

Biosimilar / COVID-19 vaccines: a global case study in rapid regulatory coordination.

The pandemic like COVID-19 created an urgent need for unprecedented global regulatory coordination, especially for vaccines and biosimilars (e.g., diagnostics, ventilators, PPE). It demonstrated how regulators can harmonize, converge, and rely on one another to speed up access while maintaining safety and efficacy standards.

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3.3 Research Methodology Options

Comparative case studies across regulatory jurisdictions.

Comparative case studies provide a rich, context sensitive methodology for analyzing how international regulatory harmonization plays out across jurisdictions. By examining similarities and differences in implementation of ICH or international agreements, researchers can draw evidence based conclusions about effectiveness, challenges, and best practices**.**

Quantitative analysis: timelines, cost differences, or number of regulatory requirements across countries.

Quantitative analysis of timelines, costs, and regulatory requirements is a powerful method for evaluating the impact of harmonization efforts like ICH guidelines. It enables policymakers and researchers to assess efficiency, effectiveness, and equity in regulatory processes across jurisdictions.

Stakeholder interviews: regulators, industry professionals, global health NGOs.

Stakeholder interviews offer rich, nuanced insights into how international regulatory frameworks are perceived and implemented. When used alongside document or quantitative analysis, they provide a comprehensive understanding of harmonization challenges and opportunities.

3.4 Results and discussions:

The Results and Discussion section suitable for a report or policy paper on dossier filing and approval harmonization of biosimilars intended for submission to a state regulatory body**.**

Long-Term Impact

- Promote domestic innovation
- Reduce time to market
- Lower costs for healthcare systems
- Increase patient access to high quality therapies and medical technologies

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4.0 Plan of work (using Gantt chart)

S. No	Activity list	Start Month	End Month	Duration	Status	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Jan-26	Feb-26	Mar-26	Apr-26	May-26	Jun-26	Jul-26	Aug-26	Sep-26	Oct-26	Nov-26	Dec-26	Jan-27	Feb-27	Mar-27	Apr-27
1	Regulatory Convergence and Harmonization	Aug-25	Oct-25	90	Pending	Pending	Pending	Pending																		
2	Case Studies	Nov-25	Jan-26	90	Pending				Pending	Pending	Pending															
3	Comparative case studies across regulatory jurisdictions	Feb-26	May-26	120	Pending							Pending	Pending	Pending	Pending											
4	Quantitative analysis: timelines, cost differences, or number of regulatory requirements across countries	Jun-26	Sep-26	120	Pending											Pending	Pending	Pending	Pending							
5	Stakeholder interviews	Oct-26	Dec-26	90	Pending															Pending	Pending	Pending				
6	Results and discussions	Jan-27	Apr-27	120	Pending																		Pending	Pending	Pending	Pending

Work Progress: To study and Analyzing harmonization of drug approval processes: challenges, progress, and future directions in regulatory convergence for stringent markets

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